Remarks/Arguments

Claims 44-47 and 49-51 are pending in this application and are rejected on various grounds. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 44-47 and 49-51 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 44-47 and 49-51 remain further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

The Examiner maintained the previous rejections and cites a new reference Hu *et al.* to show that "it is noted that the literature continues to caution researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue". For the reasons outlined below, Applicants respectfully disagree.

Arguments

Applicants maintain that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the instantly claimed PRO343 antibodies of SEQ ID NO: 263.

Applicants submit that there is a positive correlation for cancer for PRO343 based on the gene amplification data namely, at least **2.00- 12.3 fold amplification in seven lung or colon tumors** and at least **2.22- 11.24 fold amplification in thirteen colon tumors**. Applicants have presented arguments why this rejection is improper in their Response dated November 9, 2005 and maintain their position for the reasons cited therein. In support of their showing that the gene amplification values for PRO343 DNA are significant in lung or colon cancer, Applicants submitted a Declaration by Dr. Audrey Goddard with their response dated March 11, 2003. Applicants submitted that the test for utility is whether it is more likely than not that gene amplification results in overexpression of the mRNA and subsequently, the protein of the gene.

In order to meet that standard, the Examiner must provide evidence that it is more likely than not that gene amplification does not result in overexpression. Applicants maintain that the Examiner has not met this burden based on references Pennica *et al.* and Konopka *et al.* because the combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. Therefore, the teachings of these two references cannot be relied upon to establish a *prima facie* showing of lack of utility.

Applicants had discussed the Chen *et al.* reference in their response dated November 9, 2005, which showed that, the analysis provided by Chen *et al.* in fact support the Applicants general proposition that, even if protein levels cannot be accurately predicted (which is not required by the utility standard), in the majority of the proteins studied, it is most likely than not that an increase in gene amplification or mRNA levels generally correlates well with increased protein levels. For example, a review of the correlation coefficient data presented in the Chen *et al.* paper indicates that, for instance, in Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform was expressed, showed that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. The data clearly met the standards for "more likely than not". Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, in 22 genes out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least one isoform. No genes showed a significant negative correlation. Thus, Table II of Chen *et al.* also provided that it is more likely than not that protein levels will correlate with mRNA expression levels. In fact, the same authors in Chen *et al.*, published the Beer *et al.* paper which described the expression of genes in adenocarcinomas as compared to protein expression. They observed that "these results suggest that the oligonucleotide microarrays provided reliable measures of gene expression" (pg 317) and further stated that "these studies indicate that many of the genes identified using gene expression profiles are likely relevant to lung adenocarcinoma." Therefore, the authors of the Chen paper clearly agreed that microarrays provided a reliable measure of the expression levels of the gene and could be used to identify genes whose overexpression is associated with tumors.

Thus, Applicants submit that when the proper legal standard is used, Chen *et al.* clearly supported the Applicants' position that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein.

Further, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. The articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed August 11, 2004) collectively teach that in general, gene amplification increases mRNA expression. Accordingly, this rejection is improper.

The Examiner cites new reference Hu *et al.* and concludes that:

> "the literature continues to caution researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.....Hu *et al.* discovered that genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section)" (emphasis added- page 4, line 19 to page 5, line 7).

Applicants respectfully submit that, contrary to the Examiner's assertion, the Hu *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO343 molecule, for the reasons outlined below.

The Hu *et al.* reference is entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (emphasis added). Therefore, as the title itself suggests, the conclusions in this reference are based upon statistical analysis of information obtained from published literature, and not from experimental data. Hu *et al.* performed statistical analysis to provide evidence for a relationship between mRNA expression and biological function of a given molecule (as in disease). The conclusions of Hu *et al.* however, only apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column).

Moreover, the analytical methods utilized by Hu *et al.* have certain statistical drawbacks, as the authors themselves admit. For instance, according to Hu *et al.*, "*different* statistical

methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). As is well known in the art, different statistical methods allow different variables to be manipulated to affect the resulting outcome. In this regard, the authors disclose that, "Initial attempts to search the literature" using the list of genes, gene names, gene symbols, and frequently used synonyms generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors add that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Hu *et al.* had to manipulate certain aspects of the input data, in order to generate, in their opinion, meaningful results. Further, because the frequency of citation for a given molecule and its relationship to disease only reflects the current research interest of a molecule, and not the true biological function of the molecule, as the authors themselves acknowledge, the "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). Therefore, based on these findings, the authors add, "[t]his may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). In other words, some molecules may have been underrepresented merely because they were less frequently cited or studied in literature compared to other more well-cited or studied genes. Therefore, Hu *et al.*'s conclusions do not represent genes in general.

Therefore, Applicants submit that, based on the nature of the statistical analysis performed herein, and in particular, based on Hu's analysis of one class of genes, namely, the estrogen receptor (ER)-positive breast tumor genes, the conclusions drawn by the Examiner, namely that, "genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease (in general)" is not reliably supported.

Therefore summarizing the conclusions drawn so far, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these isolated instances do not satisfy the Utility standard where a showing that "it is more likely than not" must be made. Such a showing to establish a proper *prima facie* case for lack of utility has clearly not been done. On the contrary, in the majority of amplified genes in the art, as exemplified by Ornstoft *et al.,* Hyman *et al.,* Pollack *et al.,* the Polakis Declaration, etc. overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, the references cited by the Examiner, namely, Pennica *et al.*, Konopka *et al.*, Chen *et al.* and Hu *et al.*, are not sufficient to establish a *prima facie* case of lack of utility since they do not teach anything whatsoever about the correlation of protein expression and gene amplification for genes in general.

In further support of their assertion that there is "good correlation between mRNA levels and protein abundance," Applicants previously presented a Declaration by Dr. Paul Polakis (made of record in Response filed August 11, 2004; for immediate reference, see Exhibit A of attached Declaration). However, the Examiner rejected the teachings of the Polakis Declaration.

Without acquiescing to the propriety of this rejection, and merely to expedite prosecution in this case, Applicants present a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "~~A~~ as such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA. Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

Applicants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (i.e., that it is more likely than not informative of the protein level).

Thus, together, Applicants submit that the teachings of the Examiner's cited references do not conclusively establish a *prima facie* case for lack of utility because the references are, either not contrary to the Applicants' arguments, or, actually lend support to the Applicants ' position, or are not applicable to the present application due to limitations in the study, as is discussed in detail below. Applicants add that while the literature indicates that **some** references demonstrate a positive correlation between mRNA expression and protein levels, while **some** show no correlation, there are more cases in literature that show a positive correlation than not. Therefore one skilled in the art would agree based on the DNA gene amplification results that, there will "most likely" be increases in mRNA and in turn, increases in protein expression in these human cancers. Therefore, based on the claimed utility for the PRO343 polypeptide and its antibodies in the diagnosis of lung or colon cancer, the collective teachings in the specification and in the art at the time of filing, one of skill in the art would know exactly how to make and use the claimed polypeptide for the diagnosis of lung or colon cancer. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility and enablement rejections should be withdrawn.

CONCLUSION

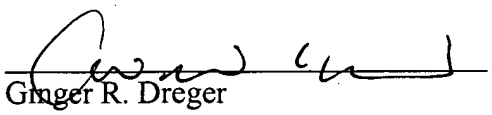
For the reasons given above, Applicants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide. As such, Applicants respectfully request reconsideration and reversal of the outstanding rejection of Claims 44-47 and 49-51 .

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any fees, including fees for extension of time or other fees, or credit any overpayment to Deposit Account No. **08-1641** referencing Attorney's Docket No. **39780-1618P2C48**.

Respectfully submitted,

Date: April 20, 2006



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